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Synthesis of cyclopropanoid analogues of *N*-acyl-muramyldipeptide as potential immunostimulants

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Abstract—The preparation of diastereomerically pure cyclopropanoid muramyldipeptide analogues from suitable substituted cyclopropylamines is described.
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1. Introduction

Over the past two decades,[1] immunopharmacology has become a viable discipline in its own right. Interest in immunostimulation has beeen fuelled by advances in bacterial cell wall chemistry, by the apparent promise of experimental and clinical tumor immunology, and by the rapidly expanding knowledge of endogenous regulators and mediators of lympho-myeloid cell differentiation and cooperation.

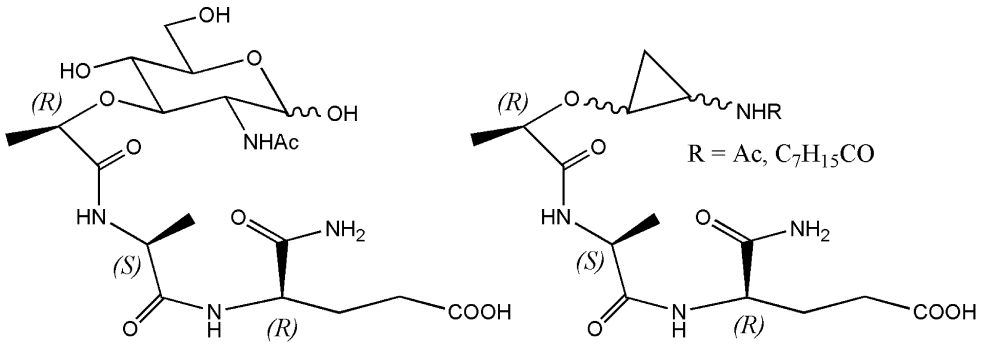
Freund's adjuvant[2,3] consisting of mycobacterial cells in a water-in-oil emulsion containing the antigen in the water phase has been used for stimulating the production of antibodies against the antigen used. Degradation of the cell walls and subjecting these fragments to a lysozyme digestion finally led to the observation that *N*-acyl-muramyl dipeptide (MDP) should be the minimal adjuvant active structure.[4,5]

In addition, MDP also has been reported[6] to enhance nonspecific immunity against viral and microbial infections[7,8] and against tumors.[9] However, MDP also induces undesirable biological activities such as pyrogenicity, induction of arthritis, transient leucopenia and sensitivization to endotoxin.[10–12]

Consequently, the MDP structure has undergone extensive chemical modification in searches for biologically active analogues having fewer and more tolerable side effects.[13,14] As a novel approach toward obtaining glycopeptide adjuvants that exhibit presumably lower toxicity and/or pharmacodynamic advantages, we report the synthesis of several derivatives wherein the carbohydrate part of MDP is replaced by a cyclopropane moiety (Fig. 1).

2. Results and discussion

While most of the MDP analogues synthesized so far



MDP **cyclopropanoid MDP analogues**

Figure 1. Structure of MDP and its cyclopropanoid analogues.

Keywords: Cyclopropanes; Muramyldipeptide; Immunomodulation.
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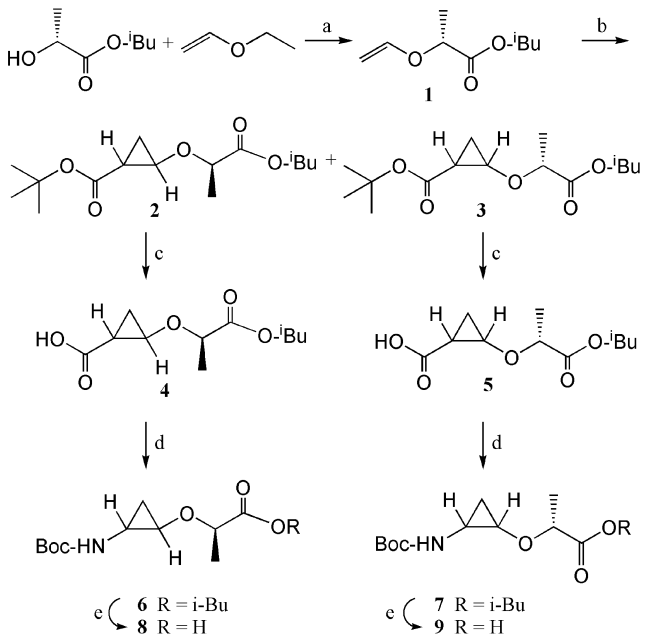
possess an intact carbohydrate-L-Ala-D-Glu-NH_2 moiety, is has been generally accepted that the *N*-acetyl-D-glucosamine fragment is not essential for the immunomodulating activity of this class[10,13,14] of compounds. Thus, replacement of the *N*-acetyl-muramyl moiety with various acyl groups represents an approach in the rational design and synthesis of new immunologically active MDP analogues, as demonstrated by some carbocyclic MDP analogues,[15–17] by the adamantyl substituted MDP analogue LK415,[18] by FK-156,[19] pimeloutide,[20] 7-(oxoacyl)-L-alanyl-D-isoglutamine[21] and even more recently by the synthesis of new lipophilic phosphonate and phosphonamidate analogues[22] or of acridine-derived compounds.[23,24]

Interestingly enough, even slight structural modifications on these compounds can lead to molecules with improved or altered pharmacological activities. Hence, the synthesis of cyclopropanoid analogues possessing either a *N*-acetyl or a *N*-octanoyl residue was envisaged. Retrosynthetic analysis revealed that these compounds should be available en route by a strategy starting from a suitable cyclopropanoid precursor (Scheme 1).



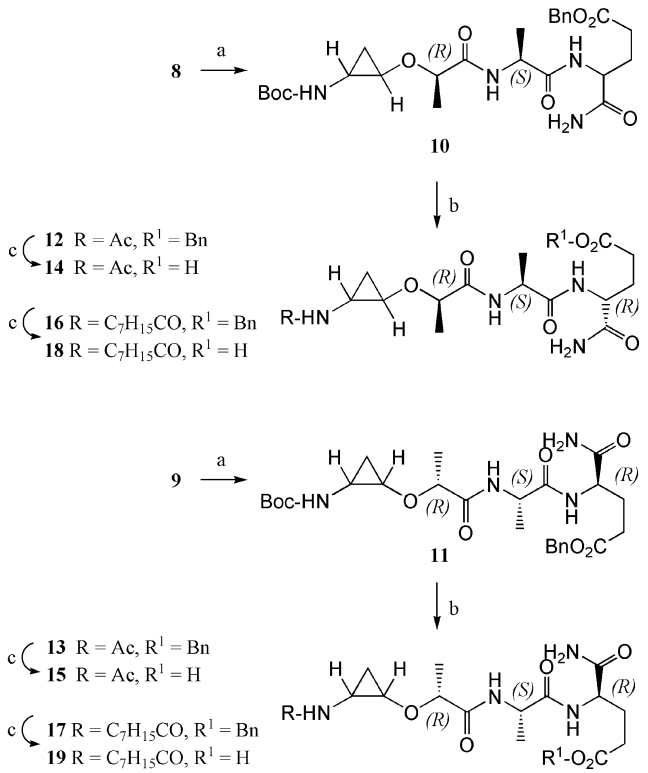
Scheme 1. Reactions and conditions: (a) $Hg(OAc)_2$; (b) N_2CHCO_2tBu, $[(Rh(OAc)_2)_2]$; (c) CF_3COOH; (d) DPPA, *t*BuOH, Et_3N; (e) KOH.

The $Hg(OAc)_2$ catalyzed reaction[25,26] between isobutyl (2*R*)-2-hydroxy-propanoate with ethyl vinyl ether resulted in the formation of 46% of isobutyl (2*R*)-2-(vinyloxy)propanoate (**1**). Although numerous methods are known for the synthesis of substituted cyclopropanes we decided to apply the $[Rh(OAc)_2]_2$ catalyzed reaction of diazoesters with olefins.[27] Thus, the reaction of **1** with *tert*-butyl diazoacetate in the presence of the rhodium catalyst gave a mixture of *trans* configurated **2** together with *cis* configurated **3**; both compounds were easily separated from each other by chromatography although they were obtained as a mixture of the corresponding diastereomers differing only in the absolute configuration at the two stereogenic centers at the cyclopropane ring.

Treatment of *trans*-**2** with trifluoroacetic acid allowed the selective cleavage[28,29] of the *tert*-butyl ester without affecting the isobutyl ester and *trans*-**4** was obtained in almost quantitative yield. Similarly, from *cis*-**3** the *cis*-configurated monoester *cis*-**5** was obtained.

Degradation of the carboxylic group was accomplished by a modified Curtius degradation[30] allowing *trans*-**4** to react with diphenylphosphoryl azide (DPPA)/*tert*-butanol in the presence of triethylamine to yield the Boc-protected amine *trans*-**6** in 55% isolated yield. Treatment of *cis*-**5** under the same conditions afforded *cis*-**7** together with 5% of *trans*-**6** that was easily separated by chromatography.

Cleavage of the ester was performed by treatment of *trans*-**6** with potassium hydroxide in ethanol and the acid *trans*-**8** was obtained as a slowly crystallizing solid that was used for the next reaction without further purification. In an analogous way, from *cis*-**7** the acid *cis*-**9** was obtained. Albeit the rather mild conditions used for this hydrolysis reaction concomitant epimerization invariably led to some extend to the formation of *trans*-**8** that had to be separated by chromatography after the next step (Scheme 2).



Scheme 2. Reactions and conditions: (a) $ClCO_2iBu$, NMM, L-Ala-D-iGln·HCl; (b) HCl in EtOAc then AcCl/Et_3N (for **12** and **13**) or $C_7H_{15}COCl/Et_3N$ (for **16** and **17**); (c) Pd/C, H_2.

Although there are a quite a number of different methods for the formation of peptide bonds, preliminary screening showed the mixed-anhydride method to work best for these reactions. The reaction of the acid *trans*-**8** with isobutyl chloroformate/*N*-methyl-morpholine[31] followed by the addition of L-alanyl-D-*iso*-glutamine-γ-benzyl ester (that was freshly prepared from commercially available Boc-L-Ala-D-isoGlnOBn by acidic cleavage of the Boc

group by reaction with hydrochloric acid in ethyl acetate) finally afforded the valuable intermediate *trans*-**10** in 86% yield. Similarly, from *cis*-**9** the protected dipeptide *cis*-**11** was obtained in 60% yield. Treatment of *trans*-**10** with hydrochloric acid in ethyl acetate followed by acetylation with acetyl chloride/triethylamine gave the *trans* configurated diasteromers **12a** and **12b**. In an analogous way from *cis*-**11** acetylated *cis*-**13** was obtained. Final deprotection was achieved by hydrogenolysis. Thus, from *trans*-**12a**,**b** the cyclopropyl analogues *trans*-**14a**,**b** were obtained and from *cis*-**13** compound *cis*-**15** was prepared in 88% yield.

It has been assumed that lipophilic MDP derivatives induce cellular-specific response and increase non-specific resistance more strongly although these derivatives are often less good adjuvants for humoral response than MDP itself.[32] In order to prepare more lipophilic compounds the Boc protecting group in *trans*-**10** was cleaved off followed by acylation with octanoyl chloride/triethylamine to afford a mixture of diastereomers *trans*-**16a** and *trans*-**16b** that were separated by chromatography. Similaryl, from *cis*-**11** the products *cis*-**17a** and *cis*-**17b** were obtained. Hydrogenolysis of **16a**,**b** and **17a**,**b** finally resulted in the formation of *cis*-**18a**, *cis*-**18b**, *trans*-**19a** and *trans*-**19b**, respectively.

Although the absolute configuration of the target molecules concerning the stereogenic centers at the cyclopropane ring remains unclear, comparison of the specific rotation values of these compounds with those reported for carbocyclic normuramyldipeptide analogues as well as with the reported values for MDP and nor-MDP suggests for **18a** a (*S*,*S*) and for **18b** a (*R*,*R*) configuration at the cyclopropane ring.

The determination of the different biological activities of the prepared carbocyclic cyclopropanoid MDP analogues is still in progress and will be reported in due course.

3. Experimental

3.1. General

Melting points are uncorrected (Leicahot stage microscope), optical rotations were obtained using a Perkin–Elmer 341 polarimeter (1 cm micro cell), NMR spectra were recorded using the Varian spectrometers Gemini 200, Gemini 2000 or Unity 500 (δ given in ppm, J in Hz, internal Me_4Si or internal CCl_3F, C′ correspond to the atoms of the heterocycle), IR spectra (film or KBr pellet) on a Perkin–Elmer FT-IR spectrometer Spectrum 1000, MS spectra were taken on a Intectra GmbH AMD 402 (electron impact, 70 eV) or on a Finnigan MAT TSQ 7000 (electrospray, voltage 4.5 kV, sheath gas nitrogen) instrument; for elemental analysis a Foss-Heraeus Vario EL instrument was used; TLC was performed on silica gel (Merck 5554, detection by UV absorption or by treatment with a solution of 10% sulfuric acid, ammonium molybdate and cerium$^{(IV)}$) sulfate followed by gentle heating. The solvents were dried according to usual procedures.

3.1.1. (1*R*) 1-(Vinyloxy)ethyl-3-methyl butanoate (1). A solution of (1*R*) 1-hydroxyethyl-3-methyl-butanoate (10.96 g, 0.075 mol) and $Hg(OAc)_2$ (23.90 g, 0.075 mol) in ethylvinyl ether (225 ml, 2.35 mol) was stirred for 7 days under argon at room temperature, then quenched by the addition of hexane (225 ml). The organic phase was washed with 1M KOH (twice 25 ml each), brine (100 ml) and dried (Na_2SO_4). The solvents were removed and the residue subjected to chromatography (silica gel, hexane/ethyl acetate, 10:1) to afford **1** (5.9 g, 46%) as a colorless oil; R_f (hexane/ethyl acetate, 3:2) 0.69; $[\alpha]_D^{20}$ 63.6° (*c* 0.47, $CHCl_3$); IR (film): ν=3535w, 3120w, 2965s, 2875m, 1760s, 1735s, 1640s, 1620s, 1510w, 1470m, 1395m, 1380m, 1320m, 1280s, 1190s, 1130s, 1095s, 1050s cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.38 (dd, $^3J_{H,H}$=14.3 Hz, $^3J_{H,H}$=6.8 Hz, 1H, HC=C), 4.39 (q, $^3J_{H,H}$=6.8 Hz, 1H, H–C(2)), 4.21 (dd, $^3J_{H,H}$=14.3 Hz, $^2J_{H,H}$=−2.5 Hz, 1H, H_2C=C (*trans*)), 4.07 (dd, $^3J_{H,H}$=6.8 Hz, $^2J_{H,H}$=−2.5 Hz, 1H, H_2C=C (*cis*)), 3.97–3.89 (m, 2H, OCH_2), 1.98–1.91 (m, 1H, CH (*i*Bu)), 1.48 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me), 0.92 (d, $^3J_{H,H}$=6.6 Hz, 6H, Me (*i*Bu)); ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.1 (s, C=O), 150.4 (d, =CH), 88.6 (t, $=CH_2$), 72.8 (d, C(2)), 71.1 (t, CH_2O), 27.6 (d, CH (*i*Bu)), 18.8 (q, Me (*i*Bu)), 17.9 (q, Me); MS (GC–MS, e.i., 70 eV): *m*/*z*=172 (2%), 157 (1%), 144 (1%), 129 (1%), 117 (18%), 116 (7%), 99 (2%), 89 (11%), 71 (100%), 57 (31%). Anal. Calcd for $C_9H_{16}O_3$ (172.110): C, 62.77; H, 9.36. Found: C, 62.68; H, 9.32.

3.1.2. Isobutyl *trans*-(2*R*)-{[2-(*tert*-butyloxycarbonyl)-cyclo-propyl]-oxy}propanoate (2) and isobutyl *cis*-(2*R*)-{[2-(*tert*-butyloxycarbonyl)cyclopropyl]oxy}propanoate (3). To a solution containing **1** (5.80 g, 33.7 mmol) in abs. CH_2Cl_2 (10 ml) and [$(Rh(OAc)_2)_2$] (100 mg) under argon a solution of *tert*-butyl-diazoacetate (5.7 g, 40.1 mmol) in abs. CH_2Cl_2 (20 ml) was added within 8 h at room temperature. After the evolution of nitrogen had ceased, the solvents were removed under reduced pressure and the residue was purified by chromatography (silica gel, hexane/ethyl acetate, 16:1) to obtain *trans*-**2** (4.6 g, 48%) and *cis*-**3** (2.6 g, 27%).

Data for **2**. R_f (hexane/ethyl acetate, 3:2) 0.68; IR (film): ν=2970s, 2875m, 1750s, 1720s, 1455m, 1395s, 1370s, 1350m, 1325m, 1275m, 1225s, 1195s, 1155s, 1135s, 1105s, 1050m, 1015m, 985m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.088 (q, $^3J_{H,H}$=6.8 Hz, 1H, H–C(2), A), 4.084 (q, $^3J_{H,H}$=6.8 Hz, 1H, H–C(2), B), 3.941 (virt.-d, $^3J_{H,H}$= 6.4 Hz, 2H, CH_2O, A), 3.939 (virt.-d, $^3J_{H,H}$=6.6 Hz, 2H, CH_2O, B), 3.70–3.65 (m, 1H, H–C(1) (Cp)), 2.02–1.90 (m, 1H, CH (*i*Bu)), 1.84–1.79 (m, 1H, H–C(2) (Cp), A), 1.71–1.67 (m, 1H, H–C(2) (Cp), B), 1.402 (s, 9H, *t*Bu, A), 1.400 (s, 9H, *t*Bu, B), 1.380 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me, A), 1.373 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me, B), 1.26–1.12 (m, 2H, $H_{A,B}$–C(3) (Cp)), 0.932 (d, $^3J_{H,H}$=6.6 Hz, 6H, Me (*i*Bu), A), 0.924 (d, $^3J_{H,H}$=6.8 Hz, 6H, Me (*i*Bu), B); ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.8 (s, C=O, A), 172.7 (s, C=O, B), 171.6 (s, C=O), 80.5 (s, *t*Bu, A), 80.4 (s, *t*Bu, B), 75.4 (d, C(2), A), 75.3 (d, C(2), B), 71.0 (t, CH_2O, A), 70.9 (t, CH_2O, B), 59.6 (d, C(1) (Cp), A), 59.5 (d, C(1) (Cp), B), 28.0 (q, *t*Bu), 27.60 (d, CH (*i*Bu), A), 27.57 (d, CH (*i*Bu), B), 22.3 (d, C(2) (Cp), A), 21.9 (d, C(2) (Cp), B), 18.9 (q, Me (*i*Bu), A), 18.8 (q, Me (*i*Bu), B), 18.4 (q, Me, A), 18.3 (q, Me, B), 15.4 (dd, C(3) (Cp), A), 14.5 (dd, C(3) (Cp), B); MS (GC–MS, e.i., 70 eV): *m*/*z*=271 (1%), 230 (1%), 213 (2%), 201 (1%), 185 (7%), 174 (2%), 147 (10%), 129 (9%), 101 (8%), 91 (25%),

84 (30%), 57 (100%). Anal. Calcd for $C_{15}H_{26}O_5$ (286.178): C, 62.91; H, 9.15. Found: C, 62.70; H, 9.05.

Data for **3**. R_f (hexane/ethyl acetate, 3:2) 0.64; IR (film): ν=3440w, 2970s, 1730s, 1455m, 1380s, 1205s, 1145s, 1055m, 985m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=4.05 (q, $^3J_{H,H}$=6.8 Hz, 1H, H–C(2), A), 4.00–3.90 (m, 2H, CH_2O), 3.88 (q, $^3J_{H,H}$=6.8 Hz, 1H, H–C(2), B), 3.79–3.75 (m, 1H, H–C(1) (Cp), A), 3.75–3.70 (m, 1H, H–C(1) (Cp), B), 2.00–1.90 (m, 1H, CH (*i*Bu)), 1.71–1.67 (m, 1H, H–C(2) (Cp), A), 1.59–1.56 (m, 1H+1H, H–C(2) (Cp), B, H_A–C(3) (Cp), A), 1.46 (s, 9H, *t*Bu, A), 1.43 (s, 9H, *t*Bu, B), 1.41–1.36 (m, 1H, H_A–C(3) (Cp), B), 1.36 (d, $^3J_{H,H}$= 7.0 Hz, 3H, Me, A), 1.34 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me, B), 1.09–1.01 (m, 1H, H_B–C(3) (Cp), A), 0.93 (d, $^3J_{H,H}$= 6.8 Hz, 6H, Me (*i*Bu), A), 0.92 (d, $^3J_{H,H}$=6.6 Hz, 6H, Me (*i*Bu), B), 0.90–0.85 (m, 1H, H_B–C(3) (Cp), B); ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.8 (s, C=O), 169.0 (s, C=O, A), 168.5 (s, C=O, B), 80.27 (s, *t*Bu, A), 80.24 (s, *t*Bu, B), 75.4 (d, C(2), A), 74.7 (d, C(2), B), 70.8 (t, CH_2O, A), 70.7 (t, CH_2O, B), 58.3 (d, C(1) (Cp), A), 56.8 (d, C(1) (Cp), B), 27.89 (q, *t*Bu, A), 27.86 (q, *t*Bu, B), 27.5 (d, CH (*i*Bu)), 22.7 (d, C(2) (Cp), A), 21.4 (d, C(2) (Cp), B), 18.78 (q, Me (*i*Bu), A), 18.77 (q, Me (*i*Bu), B), 18.4 (q, Me, A), 17.8 (q, Me, B), 13.3 (dd, C(3) (Cp), A), 11.5 (dd, C(3) (Cp), B); MS (GC–MS, e.i., 70 eV): *m*/*z*=230 (1%), 213 (2%), 201 (1%), 185 (1%), 174 (2%), 156 (3%), 147 (6%), 129 (18%), 117 (2%), 101 (8%), 91 (20%), 84 (25%), 73 (10%), 57 (100%). Anal. Calcd for $C_{15}H_{26}O_5$ (286.178): C, 62.91; H, 9.15. Found: C, 62.87; H, 9.08.

3.1.3. *trans*-2-{[(1*R*)-2-Isobutoxy-1-methyl-2-oxoethyl]-oxy}-1-cyclopropanecarboxylic acid (4). To a solution of **2** (4.07 g, 14.2 mmol) in abs. CH_2Cl_2 (40 ml) at 0 °C under argon a solution of CF_3COOH (8.10 g, 71.0 mmol) in abs. CH_2Cl_2 (7 ml) was added slowly and stirring continued for another 18 h, then the solvents were removed under diminished pressure, toluene (twice 50 ml) was added, and again the solvent was removed. Compound **4** (3.3 g, 100%) was obtained as a slightly brown oil that was used without any further purification for the next step; IR (film): ν=2965s, 2875m, 1750s, 1695s, 1450s, 1370m, 1310m, 1285m, 1200s, 1175s, 1135s, 1050m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=8.35 (br, 1H, COOH), 4.11 (q, $^3J_{H,H}$=6.8 Hz, 1H, H–C(2), A), 4.09 (q, $^3J_{H,H}$=6.8 Hz, 1H, H–C(2), B), 3.98–3.90 (m, 2H, CH_2O), 3.83–3.80 (m, 1H, H–C(1) (Cp), A),), 3.77–3.74 (m, 1H, H–C(1) (Cp), B), 2.00–1.90 (m, 1H, CH (*i*Bu)), 1.92–1.88 (m, 1H, H–C(2) (Cp), A), 1.78–1.73 (m, 1H, H–C(2) (Cp), B), 1.43–1.23 (m, 2H, $H_{A,B}$–C(3) (Cp)), 1.39 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me, A), 1.37 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me, B), 0.92 (d, $^3J_{H,H}$= 6.6 Hz, 6H, Me (*i*Bu)); ^{13}C NMR (100 MHz, $CDCl_3$): δ=178.6 (s, C=O), 172.67 (s, C=O, A), 172.58 (s, C=O, B), 75.6 (d, C(2), A), 75.4 (d, C(2), B), 71.2 (t, CH_2O, A), 71.1 (t, CH_2O, B), 60.6 (d, C(1) (Cp), A), 60.4 (d, C(1) (Cp), B), 27.6 (d, CH (*i*Bu), A), 27.5 (d, CH (*i*Bu), B), 21.1 (d, C(2) (Cp), A), 20.9 (d, C(2) (Cp), B), 18.82 (q, Me (*i*Bu), A), 18.80 (q, Me (*i*Bu), B), 18.4 (q, Me, A), 18.1 (q, Me, B), 16.5 (dd, C(3) (Cp), A), 15.6 (dd, C(3) (Cp), B); MS (e.i., 70 eV): *m*/*z*=230 (1%), 213 (2%), 201 (2%), 185 (4%), 174 (3%), 156 (3%), 147 (7%), 129 (12%), 117 (5%), 101 (9%), 91 (20%), 85 (16%), 69 (21%), 57 (100%); HRMS Calcd for $C_{11}H_{18}O_5$: 230.1154. Found: 230.1155.

3.1.4. *cis*-2-{[(1*R*)-2-Isobutoxy-1-methyl-2-oxoethyl]-oxy}-1-cyclopropanecarboxylic acid (5). Following the synthesis of **4** starting from **3** (2.40 g, 8.4 mmol) in abs. CH_2Cl_2 (30 ml) and CF_3COOH (5.70 g, 50.0 mmol) in abs. CH_2Cl_2 (5 ml) compound **5** (1.90 g, 100%) was obtained as a slightly brown oil that was used without further purification in the next step. IR (film): ν=2965s, 2875m, 2690w, 1745s, 1705s, 1455s, 1370m, 1350m, 1280m, 1210s, 1135s, 1050m, 965s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=9.15 (br, 1H, COOH), 4.10 (q, $^3J_{H,H}$=7.0 Hz, 1H, H–C(2), A), 4.00–3.84 (m, 1H+2H+1H, H–C(2), B, CH_2O, H–C(1) (Cp)), 2.00–1.88 (m, 1H, CH (*i*Bu)), 1.82–1.76 (m, 1H, H–C(2) (Cp), A), 1.72–1.62 (m, 1H, H–C(2) (Cp), B), 1.52–1.48 (m, 1H, H_A–C(3) (Cp), A), 1.44–1.39 (m, 1H, H_A–C(3) (Cp), B), 1.38 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me, A), 1.36 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me, B), 1.24–1.18 (m, 1H, H_B–C(3) (Cp), A), 1.11–1.04 (m, 1H, H_B–C(3) (Cp), B), 0.917 (d, $^3J_{H,H}$=6.6 Hz, 6H, Me (*i*Bu), A, B), 0.913 (d, $^3J_{H,H}$=6.6 Hz, 6H, Me (*i*Bu), A, B), 0.911 (d, $^3J_{H,H}$=6.8 Hz, 6H, Me (*i*Bu), A, B); ^{13}C NMR (50 MHz, $CDCl_3$): δ=178.1 (s, C=O), 172.6 (s, C=O), 172.5 (s, C=O), 75.7 (d, C(2), A), 75.4 (d, C(2), B), 71.2 (t, CH_2O, A), 71.1 (t, CH_2O, B), 59.3 (d, C(1) (Cp), A), 58.2 (d, C(1) (Cp), B), 27.7 (d, CH (*i*Bu)), 21.4 (d, C(2) (Cp), A), 20.2 (d, C(2) (Cp), B), 18.9 (q, Me (*i*Bu)), 18.6 (q, Me, A), 18.0 (q, Me, B), 14.9 (dd, C(3) (Cp), A), 13.3 (dd, C(3) (Cp), B); MS (e.i., 70 eV): *m*/*z*=231 (1%), 212 (2%), 201 (1%), 186 (2%), 175 (2%), 156 (6%), 145 (8%), 129 (43%), 117 (4%), 101 (18%), 91 (33%), 85 (81%), 73 (33%), 57 (100%); HRMS Calcd for $C_{11}H_{18}O_5$: 230.1154. Found: 230.1154.

3.1.5. *trans*-Isobutyl (2*R*)-2-({2-[*tert*-butoxycarbonyl)-amino] cyclopropyl}oxy)propanoate (6). To a solution of **4** (2.70 g, 11.7 mmol) in triethylamine (1.78 g, 17.6 mmol) and *tert*-butanol (4.33 g, 58.5 mmol) under argon diphenylphosphorylazide (3.85 g, 14.0 mmol) was added and the mixture stirred at 80 °C for 3 h; the solvents were removed and the residue was subjected to chromatography (hexane/ethyl acetate, 5:1) to afford **6** (1.9 g, 55%) as an oil; R_f (hexane/ethyl acetate, 3:2) 0.49; IR (film): ν=3370m, 2975s, 2875m, 1715s, 1505s, 1455m, 1390m, 1365s, 1255s, 1165s, 1135s, 1055m, 1020m, 990m, 945w cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=4.46 (br, 1H, NH), 4.23 (q, $^3J_{H,H}$=7.0 Hz, 1H, H–C(2), A), 3.96–3.92 (m, 1H, H–C(2), B), 3.921 (virt.-d, $^3J_{H,H}$=6.8 Hz, 2H, CH_2O, A), 3.915 (virt.-d, $^3J_{H,H}$=6.6 Hz, 2H, CH_2O, B), 3.45–3.39 (m, 1H, H–C(1) (Cp)), 2.71–2.67 (m, 1H, H–C(2) (Cp), A), 2.57–2.53 (m, 1H, H–C(2) (Cp), B), 2.00–1.90 (m, 1H, CH (*i*Bu)), 1.41 (s, 9H, *t*Bu), 1.40 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me, A), 1.37 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me, B), 1.15–1.05 (m, 1H, H_A–C(3) (Cp)), 0.933 (d, $^3J_{H,H}$= 6.8 Hz, 6H, Me (*i*Bu), A), 0.926 (d, $^3J_{H,H}$=6.6 Hz, 6H, Me (*i*Bu), B), 0.80–0.74 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.3 (s, C=O, A), 173.1 (s, C=O, B), 156.2 (s, C=O (Boc)), 79.5 (s, *t*Bu), 74.61 (d, C(2), A), 74.55 (d, C(2), B), 70.86 (t, CH_2O, A), 70.77 (t, CH_2O, B), 59.1 (d, C(1) (Cp), A), 58.8 (d, C(1) (Cp), B), 29.5 (d, C(2) (Cp)), 28.19 (q, *t*Bu, A), 28.17 (q, *t*Bu, B), 27.62 (d, CH (*i*Bu), A), 27.58 (d, CH(*i*Bu), B), 18.89 (q, Me (*i*Bu), A), 18.87 (q, Me (*i*Bu), B), 18.6 (q, Me, A), 18.1 (q, Me, B), 15.0 (dd, C(3) (Cp)); MS (e.i., 70 eV): *m*/*z*=245 (4%), 228 (1%), 200 (6%), 172 (4%), 144 (6%), 130 (11%), 116 (48%), 100 (19%), 72 (100%), 57 (100%). Anal. Calcd for

$C_{15}H_{27}O_5N$ (301.189): C, 59.78; H, 9.03; N, 4.65. Found: C, 59.86; H, 9.18; N, 4.52.

3.1.6. *cis*-Isobutyl (2*R*)-2-({2-[*tert*-butoxycarbonyl)amino]-cyclo-propyl}oxy)propanoate (7). To a solution of **5** (1.90 g, 8.25 mmol) in triethylamine (1.26 g, 12.48 mmol) and *tert*-butanol (3.07 g, 41.49 mmol) under argon diphenylphosphorylazide (2.75 g, 9.99 mmol) was added and stirring at 70 °C was continued for another 2 h, then the solvents were removed and the residue was subjected to chromatography (silica gel, hexane/ethyl acetate, 6:1) to afford 7 (0.5 g, 20%) and **6** (0.13 g, 5%, for data: vide supra) as an oil; R_f (hexane/ethyl acetate, 3:2) 0.46; IR (film): ν=3375m, 2970s, 2875m, 2150w, 1790w, 1715s, 1505s, 1470m, 1455m, 1390m, 1365s, 1255s, 1175s, 1135s, 1075m, 1055m, 985m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.32 (br, 1H, NH, A), 4.78 (br, 1H, NH, B), 4.19 (q, $^3J_{H,H}$=6.7 Hz, 1H, H–C(2), A),), 4.11 (q, $^3J_{H,H}$= 6.8 Hz, 1H, H–C(2), B), 3.99–3.87 (m, 2H, CH_2O), 3.43–3.39 (m, 1H, H–C(1) (Cp)), 2.70–2.65 (m, 1H, H–C(2) (Cp)), 2.00–1.90 (m, 1H, CH (*i*Bu)), 1.44 (s, 9H, *t*Bu, A), 1.43 (s, 9H, *t*Bu, B), 1.40 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me), 0.925 (d, $^3J_{H,H}$=6.6 Hz, 6H, Me (*i*Bu), A), 0.923 (d, $^3J_{H,H}$=6.6 Hz, 6H, Me (*i*Bu), B), 0.89–0.76 (m, 1H, H_A–C(3) (Cp)), 0.64–0.54 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (50 MHz, $CDCl_3$): δ=172.9 (s, C=O), 156.8 (s, C=O (Boc)), 79.2 (s, *t*Bu), 75.5 (d, C(2), A), 75.2 (d, C(2), B), 71.0 (t, CH_2O, A), 70.8 (t, CH_2O, B), 54.7 (d, C(1) (Cp)), 28.3 (q, *t*Bu, A), 28.2 (q, *t*Bu, B), 27.6 (d, CH (*i*Bu)), 27.4 (d, C(2) (Cp)), 18.9 (q, Me (*i*Bu)), 18.5 (q, Me, A), 18.4 (q, Me, B), 13.5 (dd, C(3) (Cp), A), 12.4 (dd, C(3) (Cp), B); MS (e.i., 70 eV): *m*/*z*=245 (4%), 228 (1%), 200 (3%), 172 (3%), 144 (12%), 130 (9%), 116 (25%), 100 (9%), 85 (5%), 72 (90%), 57 (100%). Anal. Calcd for $C_{15}H_{27}O_5N$ (301.189): C, 59.78; H, 9.03; N, 4.65. Found: C, 59.88; H, 9.16; N, 4.69.

3.1.7. *trans*-(2*R*)-2-({2-[(*tert*-Butoxycarbonyl)amino]-cyclo-propyl}oxy)propanoic acid (8). To a solution of **6** (0.5 g, 1.66 mmol) in ethanol (8 ml) at 0 °C a solution of KOH (0.3 g, 5.36 mmol) in ethanol (8 ml) was added, and the mixture stirred for 2 h at room temperature. The solvents were removed in vacuo, water (15 ml) was added to the oily residue and the pH adjusted to 3 by the careful addition of 10% aq. hydrochloric acid. The aq. phase was extracted with diethyl ether (2×20 ml) and ethyl acetate (2×20 ml), the combined organic phases were dried (Na_2SO_4), and the solvents removed to afford **8** (0.42 g, 100%) as a solid that was used in the next step without any further purification; IR (film): ν=3340m, 2980s, 2935m, 2360w, 1715s, 1515s, 1455s, 1395s, 1370s, 1255s, 1220s, 1165s, 1135s, 1055s, 950w cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.63 (br, 1H, NH), 4.48–4.40 (m, 1H, H–C(2), A), 4.36–4.28 (m, 1H, H–C(2), B), 3.47–3.39 (m, 1H, H–C(1) (Cp)), 2.72–2.68 (m, 1H, H–C(2) (Cp), A), 2.61–2.58 (m, 1H, H–C(2) (Cp), B), 1.45 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me, A), 1.431 (s, 9H, *t*Bu, A), 1.426 (s, 9H, *t*Bu, B), 1.42 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me, B), 1.19–1.07 (m, 1H, H_A–C(3) (Cp)), 0.84–0.78 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (125 MHz, $CDCl_3$): δ=176.8 (s, C=O, A), 176.4 (s, C=O, B), 156.3 (s, C=O (Boc)), 80.0 (s, *t*Bu), 74.5 (d, C(2)), 59.1 (d, C(1) (Cp), A), 58.9 (d, C(1) (Cp), B), 29.5 (d, C(2) (Cp), A), 29.3 (d, C(2) (Cp), B), 28.3 (q, *t*Bu), 18.5 (q, Me, A), 18.0 (q, Me, B), 15.1 (dd, C(3) (Cp)); MS (e.i., 70 eV): *m*/*z*=245 (1%), 230 (1%), 189 (7%), 172 (1%), 144 (5%), 128 (1%), 116 (79%), 100 (9%), 72 (79%), 57 (100%); HRMS Calcd for $C_{11}H_{19}O_5N$: 245.1263. Found: 245.1262.

3.1.8. *cis*-(2*R*)-2-({2-[(*tert*-Butoxycarbonyl)amino]cyclo-propyl}oxy)propanoic acid (9). Following the synthesis of **8** from **7** (480 mg, 1.59 mmol) in ethanol (5 ml) and KOH (280 mg, 5.00 mmol) in ethanol (7 ml) **9** (400 mg, 100%) was obtained as a brown oil that was used direct for the next step; IR (KBr): ν=3360s, 2980s, 2935m, 1720s, 1680s, 1520s, 1460m, 1395m, 1370s, 1325m, 1285s, 1250s, 1170s, 1135s, 1105m, 1085s, 1055m, 1035m, 1005m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.04 (br, 1H, NH, A), 4.80 (br, 1H, NH, B), 4.23 (q, $^3J_{H,H}$=6.5 Hz, 1H, H–C(2)), 3.47–3.39 (m, 1H, H–C(1) (Cp)), 2.70–2.59 (m, 1H, H–C(2) (Cp)), 1.45 (d, $^3J_{H,H}$=6.6 Hz, 3H, Me), 1.448 (s, 9H, *t*Bu), 1.00–0.95 (m, 1H, H_A–C(3) (Cp)), 0.69–0.60 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, $CDCl_3$): δ=176.3 (s, C=O), 155.8 (s, C=O (Boc)), 79.9 (s, *t*Bu), 75.3 (d, C(2), A), 75.0 (d, C(2), B), 54.9 (d, C(1) (Cp)), 28.4 (q, *t*Bu), 27.4 (d, C(2) (Cp)), 18.3 (q, Me, A), 18.0 (q, Me, B), 13.5 (dd, C(3) (Cp), A), 12.5 (dd, C(3) (Cp), B); MS (e.i., 70 eV): *m*/*z*=189 (4%), 172 (3%), 144 (4%), 126 (3%), 116 (57%), 100 (5%), 72 (49%), 57 (100%); HRMS Calcd for $C_{11}H_{19}O_5N$: 245.1263. Found: 245.1262.

3.1.9. Benzyl *N*-{*trans*-(2*R*)-2[2(*tert*-butoxycarbonyl-amino)cyclopropyloxy]propionyl}-L-alanyl-D-isoglutaminate (10). To a solution of Boc-L-alanyl-D-isoglutamin-γ-benzylester (40 mg, 1.57 mmol, Bachem) in abs. ethyl acetate (4 ml) a solution of hydrochloric acid in abs. ethyl acetate (ca. 3.6 N by titration, 2.7 ml, 9.7 mmol) was added and stirred at ambient temperature for 2 h, the volatiles were removed under reduced pressure and the semi-solid residue used in the next step without any further purification. To a solution of **8** (350 mg, 1.43 mmol) in abs. ethyl acetate (6 ml) and abs. DMF (6 ml) under argon at 0 °C *N*-methyl-morpholine (NMM, 159 mg, 1.57 mmol) was added, the mixture cooled to −15 °C and isobutyl chloroformate (214 mg, 1.57 mmol) was added. Stirring at this temperature was continued for another 5 min and then a solution of L-alanyl-D-isoglutamine-γ-benzylester hydro-chloride (vide supra, 539 mg, 1.57 mmol) in NMM (318 mg, 3.14 mmol), ethyl acetate (4 ml) and DMF (2 ml) was added. Stirring was continued for another 18 h at room temperature, the solvents were removed under reduced pressure, water (20 ml) was added and the aq. phase extracted with ethyl acetate (4×40 ml). The combined organic phases were dried (Na_2SO_4), the solvents were removed and the residue was subjected to chromatography (silica gel, ethyl acetate/methanol, 12:1) and **10** (660 mg, 86%) was obtained as a white amorphous solid; R_f (ethyl acetate/methanol 10:1) 0.4; IR (KBr): ν=3410m, 2980w, 1665s, 1520s, 1455m, 1365m, 1255m, 1165s cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.52 (br, 1H, NH), 7.37–7.28 (m, 5H, Ph), 7.10 (d, $^3J_{H,H}$=7.0 Hz, 1H, NH, A), 7.09 (d, $^3J_{H,H}$=8.0 Hz, 1H, NH, B), 6.82 (br, 1H, $CONH_2$), 5.41 (br, 1H, $CONH_2$), 5.11 (AB system, $^2J_{H,H}$=12.3 Hz, 2H, CH_2Ph), 4.70 (br, 1H, NH (Boc), A), 4.63 (br, 1H, NH (Boc), B), 4.46–4.39 (m, 1H, CH (*i*Gln)), 4.30–4.15 (m, 1H+1H, CH (Lac), CH (Ala)), 3.40–3.36 (m, 1H, H–C(1) (Cp), A), 3.36–3.32 (m, 1H, H–C(1) (Cp), B), 2.71–2.66 (m, 1H, H–C(2) (Cp), A), 2.61–

2.54 (m, 1H+1H, H_A–C(4) (*i*Gln), H–C(2) (Cp), B), 2.48–2.41 (m, 1H, H_B–C(4) (*i*Gln)), 2.26–2.18 (m, 1H, H_A–C(3) (*i*Gln)), 2.06–1.99 (m, 1H, H_B–C(3) (*i*Gln)), 1.41 (s, 9H, *t*Bu), 1.37 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me), 1.36 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me), 1.35 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me), 1.33 (d, $^3J_{H,H}$=6.6 Hz, 3H, Me), 1.10–1.02 (m, 1H, H_A–C(3) (Cp)), 0.81–0.74 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.8 (s, C=O), 173.5 (s, C=O), 173.4 (s, C=O), 172.8 (s, C=O), 156.8 (s, C=O (Boc), A), 156.6 (s, C=O (Boc), B), 135.8 (s, Ph), 128.6 (d, Ph), 128.34 (d, Ph), 128.29 (d, Ph), 79.9 (s, *t*Bu), 76.2 (d, C(2) (Lac), A), 75.9 (d, C(2) (Lac), B), 66.5 (t, CH_2Ph), 59.2 (d, C(1) (Cp)), 52.3 (d, C(2) (*i*Gln)), 49.3 (d, C(2) (Ala)), 30.5 (t, C(4) (*i*Gln)), 29.4 (d, C(2) (Cp)), 28.3 (q, *t*Bu, A), 28.2 (q, *t*Bu, B), 26.6 (t, C(3) (*i*Gln)), 17.7 (q, Me), 17.3 (q, Me), 14.9 (dd, C(3) (Cp)); MS (e.i., 70 eV): *m*/*z*=535 (3%), 478 (4%), 461 (2%), 390 (6%), 378 (4%), 363 (31%), 346 (34%), 299 (16%), 255 (36%), 243 (17%), 237 (27%), 215 (16%), 192 (56%), 127 (100%). Anal. Calcd for: $C_{26}H_{38}O_8N_4$ (534.269): C, 58.41; H, 7.16; N, 10.48. Found: C, 58.49; H, 7.01; N, 10.32.

3.1.10. Benzyl *N*-{*cis*-(2*R*)-2[2(*tert*-butoxycarbonyl-amino)cyclopropyloxy]propionyl}-L-alanyl-D-isoglutaminate (11). Following the procedure given for the preparation of **10** from **9** (390 mg, 1.59 mmol) in abs. ethyl acetate (6 ml) and abs. DMF (6 ml) and NMM (177 mg, 1.75 mmol), isobutyl chloroformate (239 mg, 1.75 mmol) and L-alanyl-D-isoglutamin-γ-benzylester hydrochloride [601 mg, 1.75 mmol, obtained from the deprotection of Boc-L-alanyl-D-isoglutamin-γ-benzylester (712 mg, 1.75 mmol) in abs. ethyl acetate (4 ml) and HCl/ethyl acetate (ca. 3.6 N by titration, 2.9 ml, 10.0 mmol)] in NMM (354 mg, 3.5 mmol), ethyl acetate (4 ml) and DMF (4 ml) followed by chromatography (silica gel, ethyl acetate/methanol, 12:1) **11** (500 mg, 60%) was obtained as a white solid; R_f (ethyl acetate/methanol, 10:1) 0.32. In addition, compound **10** (90 mg, 11%) was isolated; IR (KBr): ν=3405m, 2980w, 1675s, 1520s, 1455m, 1365m, 1255m, 1170s cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.47–7.42 (m, 1H+1H, NH (*i*Gln), NH (Ala), A), 7.34–7.26 (m, 5H+1H, Ph, NH (Ala), B), 6.79 (br, 1H, $CONH_2$), 5.96 (br, 1H, $CONH_2$), 5.08 (AB system, $^2J_{H,H}$=12.3 Hz, 2H, CH_2Ph), 5.03 (br, 1H, NH), 4.46–4.42 (m, 1H, CH (*i*Gln)), 4.38–4.35 (m, 1H, CH (Ala)), 4.06 (q, $^3J_{H,H}$=7.0 Hz, 1H, CH (Lac), A), 4.02 (q, $^3J_{H,H}$=7.0 Hz, 1H, CH (Lac), B), 3.34–3.31 (m, 1H, H–C(1) (Cp)), 2.63–2.60 (m, 1H, H–C(2) (Cp)), 2.60–2.48 (m, 1H, H_A–C(4) (*i*Gln)), 2.45–2.39 (m, 1H, H_B–C(4) (*i*Gln)), 2.21–2.16 (m, 1H, H_A–C(3) (*i*Gln)), 2.01–1.95 (m, 1H, H_B–C(3) (*i*Gln)), 1.42 (s, 9H, *t*Bu, A), 1.41 (s, 9H, *t*Bu, B), 1.38–1.34 (m, 6H, Me (Ala), Me (Lac)), 0.95–0.91 (m, 1H, H_A–C(3) (Cp)), 0.62–0.59 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.8 (s, C=O), 173.5 (s, C=O), 172.8 (s, C=O), 157.1 (s, C=O (Boc)), 135.8 (s, Ph), 128.7 (d, Ph), 128.4 (d, Ph), 128.3 (d, Ph), 79.8 (s, *t*Bu), 76.9 (d, C(2) (Lac)), 66.58 (t, CH_2Ph, A), 66.57 (t, CH_2Ph, B), 54.64 (d, C(1) (Cp), A), 54.60 (d, C(1) (Cp), B), 52.3 (d, C(2) (*i*Gln)), 49.1 (d, C(2) (Ala), A), 49.0 (d, C(2) (Ala), B), 30.5 (t, C(4) (*i*Gln)), 28.2 (q, *t*Bu), 26.8 (t, C(3) (*i*Gln)), 18.0 (q, Me), 17.4 (q, Me), 12.9 (dd, C(3) (Cp), A), 12.4 (dd, C(3) (Cp), B); MS (e.i., 70 eV): *m*/*z*=535 (1%), 514 (8%), 488 (1%), 435 (1%), 390 (3%), 370 (4%), 363 (6%), 346 (12%), 299 (4%), 270 (4%), 255 (23%), 237 (20%), 192 (39%), 127 (100%). Anal. Calcd for $C_{26}H_{38}O_8N_4$ (534.269): C, 58.41; H, 7.16; N, 10.48. Found: C, 58.38; H, 6.98; N, 10.69.

3.1.11. Benzyl *N*-{*trans*-(2*R*)-2[2-acetylamino-cyclopropyloxy]propionyl}-L-alanyl-D-isoglutaminate (12). A solution of **10** (600 mg, 1.12 mmol) in ethyl acetate (7 ml) was treated with a solution of hydrochloric acid in ethyl acetate (ca. 3.6 N by titration, 5 ml, 18 mmol). After stirring for 3 h at room temperature all volatiles were removed under diminished pressure. The residue was suspended in a mixture of triethylamine (963 mg, 9.5 mmol) and CH_2Cl_2 (9 ml), cooled to 0 °C and a cold solution of acetyl chloride (264 mg, 3.4 mmol) in CH_2Cl_2 (3 ml) was added dropwise, stirring was continued for 14 h at room temperature, the solvents were removed and water (30 ml) was added to the residue. The solution was extracted with ethyl acetate (4×40 ml), the combined organic phases were dried (Na_2SO_4), the solvents removed, and the residue was subjected to chromatography (silica gel, ethyl acetate/methanol, 10:1) to afford diastereomers **12a** (125 mg, 23%) and **12b** (165 mg, 31%) together with a mixture of **12a/12b** (118 mg, 22%).

Data for **12a**. White solid; mp: 125–130 °C; R_f (ethyl acetate/methanol, 3:1) 0.39; $[\alpha]_D$ 33.4° (*c* 0.62, MeOH); IR (KBr): ν=3405s, 3280s, 3070w, 2930w, 1735m, 1645s, 1545s, 1450m, 1370m, 1295m, 1245m, 1165m, 1095m, 1040w cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.74 (d, $^3J_{H,H}$=6.6 Hz, 1H, NH), 7.34–7.30 (m, 5H, Ph), 7.25 (br, 1H, NH), 7.00 (br, 1H, NH), 5.93 (br, 1H, NH), 5.67 (br, 1H, NH), 5.10 (AB system, $^2J_{H,H}$=12.3 Hz, 2H, CH_2Ph), 4.37–4.34 (m, 1H, CH (*i*Gln)), 4.34 (q, $^3J_{H,H}$=6.6 Hz, 1H, CH (Lac)), 4.16 (qd, $^3J_{H,H}$=6.9 Hz, 1H, CH (Ala)), 3.30–3.26 (m, 1H, H–C(1) (Cp)), 2.67–2.62 (m, 1H, H–C(2) (Cp)), 2.59–2.52 (m, 1H, H_A–C(4) (*i*Gln)), 2.49–2.41 (m, 1H, H_B–C(4) (*i*Gln)), 2.25–2.18 (m, 1H, H_A–C(3) (*i*Gln)), 2.09–1.99 (m, 1H, H_B–C(3) (*i*Gln)), 1.93 (s, 3H, Ac), 1.33 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me (Ala)), 1.30 (d, $^3J_{H,H}$=6.6 Hz, 3H, Me (Lac)), 1.16–1.10 (m, 1H, H_A–C(3) (Cp)), 0.90–0.82 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=176.3 (s, C=O), 175.6 (s, C=O), 175.4 (s, C=O), 175.0 (s, C=O), 174.3 (s, C=O), 137.7 (s, Ph), 129.7 (d, Ph), 129.3 (d, Ph), 77.0 (d, C(2) (Lac)), 67.4 (t, CH_2Ph), 59.0 (d, C(1) (Cp)), 53.6 (d, C(2) (*i*Gln)), 50.7 (d, C(2) (Ala)), 31.4 (t, C(4) (*i*Gln)), 29.7 (d, C(2) (Cp)), 27.9 (t, C(3) (*i*Gln)), 22.5 (q, Ac), 18.7 (q, Me), 17.7 (q, Me), 15.0 (dd, C(3) (Cp)); MS (e.i., 70 eV): *m*/*z*=476 (3%), 459 (1%), 432 (3%), 368 (1%), 363 (7%), 346 (17%), 328 (1%), 300 (1%), 292 (1%), 275 (1%), 255 (20%), 241 (32%), 237 (23%), 213 (46%), 192 (41%), 127 (100%). Anal. Calcd for $C_{23}H_{32}O_7N_4$ (476.227): C, 57.97; H, 6.77; N, 11.76. Found: C, 57.76; H, 6.70; N, 11.55.

Data for **12b**. Mp: 172.5–175.5 °C; R_f (ethyl acetate/methanol 3:1) 0.35; $[\alpha]_D$ 13.3° (*c* 0.63, MeOH); IR (KBr): ν=3405s, 3280s, 3070w, 2930w, 1735m, 1645s, 1545s, 1450m, 1370m, 1295m, 1245m, 1165m, 1095m, 1040w cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.69 (d, $^3J_{H,H}$=6.4 Hz, 1H, NH), 7.36–7.30 (m, 5H+1H, Ph, NH), 6.91 (br, 1H, NH), 5.83 (br, 1H, NH), 5.68 (br, 1H, NH), 5.09 (AB system, $^2J_{H,H}$=12.4 Hz, 2H, CH_2Ph), 4.43–4.38 (m, 1H, CH (*i*Gln)), 4.25–4.19 (m, 1H+1H, CH (Ala), CH

(Lac)), 3.31–3.28 (m, 1H, H–C(1) (Cp)), 2.78–2.75 (m, 1H, H–C(2) (Cp)), 2.58–2.50 (m, 1H, H_A–C(4) (*i*Gln)), 2.48–2.40 (m, 1H, H_B–C(4) (*i*Gln)), 2.26–2.19 (m, 1H, H_A–C(3) (*i*Gln)), 2.05–1.95 (m, 1H, H_B–C(3) (*i*Gln)), 1.90 (s, 3H, Ac), 1.34 (d, $^3J_{H,H}$=6.8 Hz, 3H+3H, Me (Ala), Me (Lac)), 1.11–1.06 (m, 1H, H_A–C(3) (Cp)), 0.80–0.75 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ= 176.3 (s, C=O), 175.9 (s, C=O), 175.3 (s, C=O), 174.9 (s, C=O), 174.4 (s, C=O), 137.7 (s, Ph), 129.7 (d, Ph), 129.3 (d, Ph), 77.3 (d, C(2) (Lac)), 67.4 (t, CH_2Ph), 59.5 (d, C(1) (Cp)), 53.6 (d, C(2) (*i*Gln)), 50.7 (d, C(2) (Ala)), 31.4 (t, C(4) (*i*Gln)), 29.7 (d, C(2) (Cp)), 27.9 (t, C(3) (*i*Gln)), 22.4 (q, Ac), 18.5 (q, Me), 17.8 (q, Me), 14.6 (dd, C(3) (Cp)); MS (e.i., 70 eV): *m*/*z*=476 (3%), 459 (1%), 432 (3%), 368 (1%), 363 (7%), 346 (17%), 328 (1%), 300 (1%), 292 (1%), 275 (1%), 255 (20%), 241 (32%), 237 (23%), 213 (46%), 192 (41%), 127 (100%). Anal. Calcd for $C_{23}H_{32}O_7N_4$ (476.227): C, 57.97; H, 6.77; N, 11.76. Found: C, 57.84; H, 6.85; N, 11.61.

3.1.12. Benzyl *N*-{*cis*-(2*R*)-2[2-acetylamino-cyclopropyl-oxy] propionyl}-L-alanyl-D-isoglutaminate (13). Following the procedure for the synthesis of **12** from **11** (265 mg, 0.56 mmol) in abs. ethyl acetate (3 ml), HCl in ethyl acetate (ca. 3.6 N, 0.6 ml, ca. 2.0 mmol) and CH_2Cl_2 (5 ml), triethylamine (505 mg, 5.0 mmol) and a solution of acetyl chloride (79 mg, 1 mmol) in CH_2Cl_2 (2 ml) followed by chromatography (silica gel, ethyl acetate/methanol, 10:1) **13** (171 mg, 65%) was obtained as a white solid; R_f (ethyl acetate/methanol, 10:1) 0.12; IR (KBr): ν=3415m, 3065w, 2930w, 1730m, 1660s, 1535m, 1450m, 1385m, 1260m, 1170m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.47 (d, $^3J_{H,H}$=8.0 Hz, 1H, NH, A), 7.43 (d, $^3J_{H,H}$=7.0 Hz, 1H, NH), 7.36–7.28 (m, 5H+1H, Ph, NH, B), 6.89 (br, 1H, NH, A), 6.81 (br, 1H, NH, B), 6.33 (br, 1H, NH), 5.98 (br, 1H, NH, A), 5.95 (br, 1H, NH, B), 5.09 (AB system, $^2J_{H,H}$=12.5 Hz, 2H, CH_2Ph), 4.45–4.34 (m, 1H+1H, CH (*i*Gln), CH (Ala)), 4.07 (q, $^3J_{H,H}$=6.7 Hz, 1H, CH (Lac), A), 4.01 (q, $^3J_{H,H}$= 6.9 Hz, 1H, CH (Lac), B), 3.41–3.37 (m, 1H, H–C(1) (Cp), A), 3.34–3.32 (m, 1H, H–C(1) (Cp), B), 2.87–2.81 (m, 1H, H–C(2) (Cp), A), 2.79–2.74 (m, 1H, H–C(2) (Cp), B), 2.58–2.50 (m, 1H, H_A–C(4) (*i*Gln)), 2.48–2.40 (m, 1H, H_B–C(4) (*i*Gln)), 2.23–2.14 (m, 1H, H_A–C(3) (*i*Gln)), 2.03–1.93 (m, 1H, H_B–C(3) (*i*Gln)), 1.98 (s, 3H, Ac, A), 1.96 (s, 3H, Ac, B), 1.38 (d, $^3J_{H,H}$=6.8 Hz 3H, Me), 1.35 (d, $^3J_{H,H}$=6.4 Hz, 3H, Me), 1.02–0.96 (m, 1H, H_A–C(3) (Cp)), 0.65–0.60 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=176.0 (s, C=O), 175.5 (s, C=O), 175.4 (s, C=O), 175.04 (s, C=O), 174.96 (s, C=O), 174.87 (s, C=O), 174.1 (s, C=O), 137.4 (s, Ph), 129.5 (d, Ph), 129.2 (d, Ph), 77.9 (d, C(2) (Lac), A), 77.8 (d, C(2) (Lac), B), 67.4 (t, CH_2Ph), 55.8 (d, C(1) (Cp), A), 55.5 (d, C(1) (Cp), B), 53.6 (d, C(2) (*i*Gln)), 50.5 (d, C(2) (Ala)), 31.4 (t, C(4) (*i*Gln)), 28.4 (d, C(2) (Cp)), 28.0 (t, C(3) (*i*Gln)), 22.44 (q, Ac, A), 22.40 (q, Ac, B), 18.9 (q, Me, A), 18.6 (q, Me, B), 18.0 (q, Me), 12.6 (dd, C(3) (Cp), A), 12.0 (dd, C(3) (Cp), B); MS (e.i., 70 eV): *m*/*z*=476 (1%), 432 (1%), 363 (3%), 346 (5%), 255 (18%), 241 (11%), 213 (20%), 200 (4%), 192 (16%), 127 (100%). Anal. Calcd for: $C_{23}H_{32}O_7N_4$ (476.227): C, 57.97; H, 6.77; N, 11.76. Found: C, 57.76; H, 6.78; N, 11.93.

3.1.13. *trans*-(2*R*)-2-[2-(Acetylamino)cyclopropyloxy]-propionyl-L-alanyl-D-isoglutamine (14a). Hydrogenolysis of **12a** (90 mg, 0.19 mmol) in ethanol (15 ml) with Pd/C (10%, 20 mg) was performed for 6 h at 3 bar pressure. After the completion of the reaction the catalyst was filtered off, the solvent removed and the residue purified by chromatography (silica gel, chloro-form/methanol/acetic acid, 70:25:5) to afford **14a** (62 mg, 85%) as a white solid; mp: 200–208 °C (decomp.); R_f ($CHCl_3$/MeOH/AcOH, 70:25:5) 0.30; $[\alpha]_D$ 30.6° (*c* 0.64, MeOH); IR (KBr): ν=3410s, 1660s, 1540s, 1430s, 1300m, 1180w, 1130w, 1100w, 1050w, 1020w cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ=8.51 (br, 1H, NH), 8.15 (br, 1H, NH), 8.01 (d, $^3J_{H,H}$= 7.4 Hz, 1H, NH), 7.29 (br, 1H, NH), 7.03 (br, 1H, NH), 4.23 (qd, $^3J_{H,H}$=7.1 Hz, 1H, CH (Ala)), 4.14 (q, $^3J_{H,H}$=6.64 Hz, 1H, CH (Lac)), 4.11–4.05 (m, 1H, CH (*i*Gln)), 3.38–3.33 (m, 1H, H–C(1) (Cp)), 2.60–2.57 (m, 1H, H–C(2) (Cp)), 2.10–2.04 (m, 2H, H–C(4) (*i*Gln)), 1.91–1.65 (m, 2H, H_A–C(3) (*i*Gln)), 1.75 (s, 3H, Ac), 1.23 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me), 1.19 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me), 0.99–0.94 (m, 1H, H_A–C(3) (Cp)), 0.72–0.68 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=176.9 (s, C=O), 175.7 (s, C=O), 175.1 (s, C=O), 174.9 (s, C=O), 77.0 (d, C(2) (Lac)), 59.0 (d, C(1) (Cp)), 54.5 (d, C(2) (*i*Gln)), 50.8 (d, C(2) (Ala)), 34.0 (t, C(4) (*i*Gln)), 29.8 (d, C(2) (Cp)), 29.1 (t, C(3) (*i*Gln)), 22.5 (q, Ac), 18.9 (q, Me), 17.6 (q, Me), 15.1 (dd, C(3)); HPLC-MS (ESI, 4.1 kV, 8 μl/min, N_2, methanol): *m*/*z*=849.2 $[M_2K_2-H]^+$ (31%), 425.5 $[MK]^+$ (100%); HRMS Calcd for $C_{16}H_{26}O_7N_4$: 386.1801. Found: 386.1802. Anal. Calcd for $C_{16}H_{26}O_7N_4$ (386.180): C, 49.73; H, 6.78; N, 14.50. Found: C, 49.55; H, 6.50; N, 14.36.

3.1.14. *trans*-(2*R*)-2-[2-(Acetylamino)cyclopropyloxy]-propionyl-L-alanyl-D-isoglutamine (14b). Hydrogenolysis of **12b** (140 mg, 0.29 mmol) in ethanol (15 ml) in the presence of Pd/C (10%, 20 mg) afforded after chromatography (silica gel, chloroform/methanol/acetic acid, 70:25:5) **14b** (100 mg, 88%) as a white solid; mp: 200–210 °C (decomp.); R_f ($CHCl_3$/MeOH/AcOH, 70:25:5) 0.30; $[\alpha]_D$ 13.8° (*c* 0.56, MeOH); IR (KBr): ν=3430s, 2935w, 1655s, 1560s, 1440w, 1300w, 1165w, 1045w cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ=8.50 (br, 1H, NH), 8.04 (br, 1H, NH), 7.96 (d, $^3J_{H,H}$=7.0 Hz, 1H, NH), 7.35 (br, 1H, NH), 6.99 (br, 1H, NH), 4.25 (qd, $^3J_{H,H}$=6.9 Hz, 1H, CH (Ala)), 4.10–4.04 (m, 1H, CH (*i*Gln)), 4.09 (q, $^3J_{H,H}$=6.64 Hz, 1H, CH (Lac)), 3.34–3.31 (m, 1H, H–C(1) (Cp), from the measurement in CD_3OD), 2.70–2.66 (m, 1H, H–C(2) (Cp)), 1.99 (t, $^3J_{H,H}$=7.2 Hz, 2H, H–C(4) (*i*Gln)), 1.91–1.82 (m, 1H, H_A–C(3) (*i*Gln)), 1.75–1.66 (m, 1H, H_B–C(3) (*i*Gln)), 1.74 (s, 3H, Ac), 1.21 (d, $^3J_{H,H}$=6.6 Hz, 3H+3H, Me (Ala), Me (Lac)), 0.99–0.95 (m, 1H, H_A–C(3) (Cp)), 0.72–0.68 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=177.3 (s, C=O), 176.2 (s, C=O), 175.3 (s, C=O), 175.1 (s, C=O), 77.4 (d, C(2) (Lac)), 59.7 (d, C(1) (Cp)), 54.5 (d, C(2) (*i*Gln)), 50.7 (d, C(2) (Ala)), 34.4 (t, C(4) (*i*Gln)), 29.7 (d, C(2) (Cp)), 29.2 (t, C(3) (*i*Gln)), 22.4 (q, Ac), 18.6 (q, Me), 17.6 (q, Me), 14.5 (dd, C(3)); HPLC-MS (ESI, 4.1 kV, 8 μl/min, N_2, methanol): *m*/*z*=811.0 $[M_2K]^+$ (77%), 425.1 $[MK]^+$ (100%), 409.4 $[MNa]^+$ (15%), 393.3 $[MLi]^+$ (16%); HRMS Calcd for $C_{16}H_{26}O_7N_4$: 386.1801. Found: 386.1802. Anal. Calcd for $C_{16}H_{26}O_7N_4$ (386.180): C, 49.73; H, 6.78; N, 14.50. Found: C, 49.53; H, 6.59; N, 14.68.

3.1.15. *cis*-(2*R*)-2-[2-(Acetylamino)cyclopropyloxy]propionyl-L-alanyl-D-isoglutamine (15). Hydrogenolysis of **13** (95 mg, 0.29 mmol) in ethanol (15 ml) in the presence of Pd/C (10%, 20 mg) followed by chromatography (silica gel, chloroform/methanol/acetic acid, 70:25:5) afforded **15** (100 mg, 88%) as an amorphous solid; R_f ($CHCl_3$/MeOH/AcOH, 70:25:5) 0.30; IR (KBr): ν=3425s, 3075w, 2995w, 1655s, 1540m, 1450w, 1375w, 1320s, 1235w, 1170w cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=13.0–11.0 (very br, 1H, COOH), 8.10 (d, $^3J_{H,H}$=7.8 Hz, 1H, NH, A), 8.08 (d, $^3J_{H,H}$=8.2 Hz, 1H, NH, B), 7.91 (d, $^3J_{H,H}$=4.5 Hz, 1H, NH), 7.87–7.85 (m, 1H, NH), 7.70 (d, $^3J_{H,H}$=7.2 Hz, 1H, NH), 7.33 (br, 1H, NH), 7.08 (br, 1H, NH), 4.29 (qd, $^3J_{H,H}$=6.9 Hz, 1H, CH (Ala), A), 4.28 (qd, $^3J_{H,H}$=6.9 Hz, 1H, CH (Ala), B), 4.18–4.14 (m, 1H, CH (*i*Gln)), 3.91 (q, $^3J_{H,H}$=6.6 Hz, 1H, CH (Lac), A), 3.85 (q, $^3J_{H,H}$=6.8 Hz, 1H, CH (Lac), B), 3.46–3.41 (m, 1H, H–C(1) (Cp), determined in CD_3OD), 2.62–2.57 (m, 1H, H–C(2) (Cp)), 2.18 (*virt.*-t, $^3J_{H,H}$=7.8 Hz, 2H, H–C(4) (*i*Gln)), 1.98–1.94 (m, 1H, H_A–C(3) (*i*Gln)), 1.84 (s, 3H, Ac, A), 1.78 (s, 3H, Ac, B), 1.74–1.67 (m, 1H, H_B–C(3) (*i*Gln)), 1.25 (d, $^3J_{H,H}$=6.4 Hz, 3H, Me), 1.23 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me), 1.18 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me), 0.94–0.86 (m, 1H, H_A–C(3) (Cp)), 0.68–0.64 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=176.0 (s, C=O), 175.3 (s, C=O), 174.8 (s, C=O), 77.9 (d, C(2) (Lac), A), 77.8 (d, C(2) (Lac), B), 55.8 (d, C(1) (Cp), A), 55.6 (d, C(1) (Cp), B), 53.8 (d, C(2) (*i*Gln)), 50.6 (d, C(2) (Ala)), 31.3 (t, C(4) (*i*Gln)), 28.5 (d, C(2) (Cp), A), 28.2 (t, C(3) (*i*Gln)), 28.1 (d, C(2) (Cp), B), 22.4 (q, Ac), 18.9 (q, Me), 18.6 (q, Me), 18.1 (q, Me), 12.6 (dd, C(3), A), 12.0 (dd, C(3), B); MS (e.i., 70 eV): *m*/*z*=386 (3%), 369 (1%), 342 (1%), 255 (9%), 241 (6%), 213 (9%), 200 (3%), 184 (4%), 169 (4%), 145 (12%), 127 (100%); HRMS Calcd for $C_{16}H_{26}O_7N_4$: 386.1801. Found: 386.1802. Anal. Calcd for: $C_{16}H_{26}O_7N_4$ (386.180): C, 49.73; H, 6.78; N, 14.50. Found: C, 49.69; H, 6.55; N, 14.72.

3.1.16. Benzyl *N*-{*trans*-(2*R*)-2[2-octanoylamino-cyclopropyl-oxy]propionyl}-L-alanyl-D-isoglutaminate (16). As described for the synthesis of **12** treatment of a solution of **10** (250 mg, 0.47 mmol) in abs. ethyl acetate (3 ml) with hydrochloric acid in ethyl acetate (ca. 3.6 N, 1.0 ml, ca. 3.6 mmol) followed by the reaction of the intermediary hydrochloride in CH_2Cl_2 (3 ml) with triethylamine (404 mg, 4.0 mmol) and a solution of octanoyl chloride (100 mg, 0.62 mmol) in CH_2Cl_2 (2 ml) gave after chromatography (silica gel, ethyl acetate/methanol, 9:1) the diastereomers **16a** (70 mg, 27%) and **16b** (40 mg, 15%) together with a mixture **16a/16b** (130 mg, 49%).

Data for **16a**. White solid; mp: 151–153 °C; R_f (EtOAc/MeOH 10:1) 0.27; $[\alpha]_D$ 34.9° (*c* 1.07, MeOH); IR (KBr): ν=3395s, 3270s, 3070m, 2930s, 2855m, 1740s, 1650s, 1545s, 1455m, 1375m, 1310m, 1250s, 1165s, 1095m, 1040m cm^{-1}; MS (e.i., 70 eV): *m*/*z*=560 (4%), 543 (19%), 516 (4%), 453 (1%), 363 (1%), 346 (4%), 325 (4%), 297 (21%), 282 (2%), 255 (29%), 237 (4%), 198 (5%), 183 (12%), 127 (100%); ^1H NMR (400 MHz, $CDCl_3$): δ=7.86 (d, $^3J_{H,H}$=6.5 Hz, 1H, NH), 7.39 (d, $^3J_{H,H}$=8.0 Hz, 1H, NH), 7.35–7.26 (m, 5H, Ph), 6.99 (br, 1H, NH), 6.02 (br, 1H, NH), 5.94 (br, 1H, NH), 5.09 (AB system, $^2J_{H,H}$=12.4 Hz, 2H, CH_2Ph), 4.40–4.33 (m, 1H, CH (*i*Gln)), 4.36 (q, $^3J_{H,H}$=6.4 Hz, 1H, CH (Lac)), 4.12 (qd, $^3J_{H,H}$=6.9 Hz, 1H, CH (Ala)), 3.30–3.28 (m, 1H, H–C(1) (Cp)), 2.64–2.60 (m, 1H, H–C(2) (Cp)), 2.58–2.39 (m, 2H, H–C(4) (*i*Gln)), 2.25–2.17 (m, 1H, H_A–C(3) (*i*Gln)), 2.13–2.08 (m, 2H, H–C(2) (Oct)), 2.06–1.95 (m, 1H, H_B–C(3) (*i*Gln)), 1.59–1.53 (m, 2H, H–C(3) (Oct)), 1.32 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me), 1.28 (d, $^3J_{H,H}$=6.6 Hz, 3H, Me), 1.28–1.22 (m, 8H, Oct), 1.13–1.08 (m, 1H, H_A–C(3) (Cp)), 0.89–0.79 (m, 3H+1H, Me (Oct), H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=178.1 (s, C=O), 176.3 (s, C=O), 175.7 (s, C=O), 175.4 (s, C=O), 174.4 (s, C=O), 137.7 (s, Ph), 129.7 (d, Ph), 129.3 (d, Ph), 77.0 (d, C(2) (Lac)), 67.5 (t, CH_2Ph), 59.1 (d, C(1) (Cp)), 53.6 (d, C(2) (*i*Gln)), 50.8 (d, C(2) (Ala)), 36.9 (t, C(2) (Oct)), 32.8 (t, C(3) (Oct)), 31.4 (t, C(4) (*i*Gln)), 30.2 (t, Oct), 30.0 (t, Oct), 29.7 (d, C(2) (Cp)), 27.9 (t, C(3) (*i*Gln)), 26.8 (t, Oct), 23.6 (t, Oct), 18.7 (q, Me), 17.7 (q, Me), 15.1 (dd, C(3) (Cp)), 14.3 (q, Me (Oct)). Anal. Calcd for $C_{29}H_{44}O_7N_4$ (560.321): C, 62.12; H, 7.91; N, 9.99. Found: C, 62.02; H, 7.71; N, 10.11.

Data for **16b**. White solid; mp: 135–140 °C; R_f (EtOAc/MeOH, 10:1) 0.26; $[\alpha]_D$ 15.2° (*c* 1.07, MeOH); IR (KBr): ν=3395s, 3270s, 3070m, 2930s, 2855m, 1740s, 1650s, 1545s, 1455m, 1375m, 1310m, 1250s, 1165s, 1095m, 1040m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.81 (d, $^3J_{H,H}$=6.3 Hz, 1H, NH), 7.36–7.29 (m, 5H, Ph), 7.14 (d, $^3J_{H,H}$=8.0 Hz, 1H, NH), 6.90 (br, 1H, NH), 5.57 (br, 1H, NH), 5.41 (br, 1H, NH), 5.10 (AB system, $^2J_{H,H}$=12.3 Hz, 2H, CH_2Ph), 4.44–4.38 (m, 1H, CH (*i*Gln)), 4.27 (q, $^3J_{H,H}$=6.7 Hz, 1H, CH (Lac)), 4.16 (qd, $^3J_{H,H}$=6.7 Hz, 1H, CH (Ala)), 3.31–3.28 (m, 1H, H–C(1) (Cp)), 2.82–2.79 (m, 1H, H–C(2) (Cp)), 2.60–2.52 (m, 1H, H_A–C(4) (*i*Gln)), 2.48–2.40 (m, 1H, H_B–C(4) (*i*Gln)), 2.26–2.18 (m, 1H, H_A–C(3) (*i*Gln)), 2.09 (virt.-t, $^3J_{H,H}$=7.6 Hz, 2H, H–C(2) (Oct)), 2.06–1.97 (m, 1H, H_B–C(3) (*i*Gln)), 1.59–1.54 (m, 2H, H–C(3) (Oct)), 1.35 (d, $^3J_{H,H}$=6.5 Hz, 3H, Me), 1.33 (d, $^3J_{H,H}$=6.2 Hz, 3H, Me), 1.28–1.22 (m, 8H, Oct), 1.11–1.06 (m, 1H, H_A–C(3) (Cp)), 0.85 (t, $^3J_{H,H}$=6.8 Hz, 3H, Me (Oct)), 0.78–0.74 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=177.5 (s, C=O), 175.9 (s, C=O), 175.4 (s, C=O), 174.9 (s, C=O), 173.9 (s, C=O), 137.3 (s, Ph), 129.2 (d, Ph), 128.91 (d, Ph), 128.89 (d, Ph), 76.9 (d, C(2) (Lac)), 67.0 (t, CH_2Ph), 59.2 (d, C(1) (Cp)), 53.2 (d, C(2) (*i*Gln)), 50.2 (d, C(2) (Ala)), 36.4 (t, C(2) (Oct)), 32.4 (t, C(3) (Oct)), 31.0 (t, C(4) (*i*Gln)), 29.7 (t, Oct), 29.6 (t, Oct), 29.2 (d, C(2) (Cp)), 27.5 (t, C(3) (*i*Gln)), 26.4 (t, Oct), 23.1 (t, Oct), 18.1 (q, Me), 17.3 (q, Me), 14.3 (dd, C(3) (Cp)), 13.9 (q, Me (Oct)); MS (e.i., 70 eV): *m*/*z*=560 (4%), 543 (19%), 516 (4%), 453 (1%), 363 (1%), 346 (4%), 325 (4%), 297 (21%), 282 (2%), 255 (29%), 237 (4%), 198 (5%), 183 (12%), 127 (100%). Anal. Calcd for $C_{29}H_{44}O_7N_4$ (560.321): C, 62.12; H, 7.91; N, 9.99. Found: C, 61.99; H, 7.82; N, 9.76.

3.1.17. Benzyl *N*-{*cis*-(2*R*)-2[2-octanoylamino-cyclopropyloxy]-propionyl}-L-alanyl-D-isoglutaminate (17). Following the procedure given for the synthesis of **12** from **11** (210 mg, 0.39 mmol) in abs. ethyl acetate (3 ml), hydrochloric acid in ethyl acetate (ca. 3.6 N, 0.7 ml, ca. 2.5 mmol), triethylamine (394 mg, 3.9 mmol) in CH_2Cl_2 (3 ml), and a solution of octanoyl chloride (96 mg, 0.59 mmol) in CH_2Cl_2 (1 ml) followed by chromatography (silica gel, ethyl acetate/methanol, 16:1→10:1) **17a** (60 mg,

27%) and **17b** (40 mg, 18%) together with a mixture **17a/17b** (95 mg, 43%) were obtained.

Data for **17a**. White solid; mp: 166–169 °C; R_f (EtOAc/MeOH, 10:1) 0.27; $[\alpha]_D$ −13.3° (*c* 0.36, MeOH); IR (KBr): ν=3430s, 3300m, 2930m, 2855w, 1725m, 1650s, 1540m, 1450w, 1385w, 1240w, 1175m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.45 (d, $^3J_{H,H}$=7.8 Hz, 1H, NH), 7.35–7.28 (m, 5H+1H, Ph, NH), 6.81 (br, 1H, NH), 6.07 (br, 1H, NH), 5.94 (br, 1H, NH), 5.09 (AB system, $^2J_{H,H}$=12.3 Hz, 2H, CH_2Ph), 4.45–4.40 (m, 1H, CH (*i*Gln)), 4.38 (qd, $^3J_{H,H}$=7.0 Hz, 1H, CH (Ala)), 4.00 (q, $^3J_{H,H}$=6.8 Hz, 1H, CH (Lac)), 3.40–3.36 (m, 1H, H–C(1) (Cp)), 2.88–2.82 (m, 1H, H–C(2) (Cp)), 2.58–2.50 (m, 1H, H_A–C(4) (*i*Gln)), 2.50–2.40 (m, 1H, H_B–C(4) (*i*Gln)), 2.23–2.16 (m, 1H+2H, H_A–C(3) (*i*Gln), H–C(2) (Oct)), 2.03–1.94 (m, 1H, H_B–C(3) (*i*Gln)), 1.61–1.58 (m, 2H, H–C(3) (Oct)), 1.36 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me), 1.34 (d, $^3J_{H,H}$=6.6 Hz, 3H, Me), 1.29–1.22 (m, 8H, Oct), 1.03–0.98 (m, 1H, H_A–C(3) (Cp)), 0.84 (t, $^3J_{H,H}$=6.8 Hz, 3H, Me (Oct)), 0.64–0.59 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=178.0 (s, C=O), 176.0 (s, C=O), 175.6 (s, C=O), 175.0 (s, C=O), 174.1 (s, C=O), 137.5 (s, Ph), 129.5 (d, Ph), 129.2 (d, Ph), 77.7 (d, C(2) (Lac)), 67.5 (t, CH_2Ph), 55.7 (d, C(1) (Cp)), 53.6 (d, C(2) (*i*Gln)), 50.6 (d, C(2) (Ala)), 36.8 (t, C(2) (Oct)), 32.8 (t, C(3) (Oct)), 31.4 (t, C(4) (*i*Gln)), 30.4 (t, Oct), 30.1 (t, Oct), 28.4 (t, C(3) (*i*Gln)), 28.0 (d, C(2) (Cp)), 27.0 (t, Oct), 23.6 (t, Oct), 19.0 (q, Me), 18.0 (q, Me), 14.4 (q, Me (Oct)), 11.9 (dd, C(3) (Cp)); MS (e.i., 70 eV): *m*/*z*=560 (5%), 452 (1%), 363 (1%), 346 (3%), 325 (1%), 297 (4%), 282 (1%), 255 (11%), 237 (4%), 226 (4%), 198 (6%), 192 (4%), 181 (4%), 127 (100%). Anal. Calcd for $C_{29}H_{44}O_7N_4$ (560.321): C, 62.12; H, 7.91; N, 9.99. Found: C, 61.90; H, 7.87; N, 9.74.

Data for **17b**. White solid; mp: 174–175 °C; R_f (EtOAc/MeOH, 10:1) 0.27; $[\alpha]_D$ 29.3° (*c* 0.48, MeOH); IR (KBr): ν=3430s, 3300m, 2930m, 2855w, 1725m, 1650s, 1540m, 1450w, 1385w, 1240w, 1175m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.35–7.30 (m, 5H+1H, Ph, NH), 7.14 (d, $^3J_{H,H}$=7.8 Hz, 1H, NH), 6.79 (br, 1H, NH), 5.87 (br, 1H, NH), 5.44 (br, 1H, NH), 5.10 (AB system, $^2J_{H,H}$=12.3 Hz, 2H, CH_2Ph), 4.45–4.41 (m, 1H, CH (*i*Gln)), 4.34 (qd, $^3J_{H,H}$=7.0 Hz, 1H, CH (Ala)), 4.06 (q, $^3J_{H,H}$=6.7 Hz, 1H, CH (Lac)), 3.38–3.34 (m, 1H, H–C(1) (Cp)), 2.83–2.77 (m, 1H, H–C(2) (Cp)), 2.62–2.56 (m, 1H, H_A–C(4) (*i*Gln)), 2.49–2.40 (m, 1H, H_B–C(4) (*i*Gln)), 2.21–2.15 (m, 1H+2H, H_A–C(3) (*i*Gln), H–C(2) (Oct)), 2.04–1.96 (m, 1H, H_B–C(3) (*i*Gln)), 1.62–1.58 (m, 2H, H–C(3) (Oct)), 1.40 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me), 1.37 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me), 1.28–1.22 (m, 8H, Oct), 1.03–0.98 (m, 1H, H_A–C(3) (Cp)), 0.85 (t, $^3J_{H,H}$=6.9 Hz, 3H, Me (Oct)), 0.61–0.58 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=178.5 (s, C=O), 176.3 (s, C=O), 175.8 (s, C=O), 175.2 (s, C=O), 174.4 (s, C=O), 137.7 (s, Ph), 129.7 (d, Ph), 129.4 (d, Ph), 77.9 (d, C(2) (Lac)), 67.5 (t, CH_2Ph), 55.5 (d, C(1) (Cp)), 53.6 (d, C(2) (*i*Gln)), 50.6 (d, C(2) (Ala)), 36.8 (t, C(2) (Oct)), 32.8 (t, C(3) (Oct)), 31.4 (t, C(4) (*i*Gln)), 30.2 (t, Oct), 30.1 (t, Oct), 28.02 (t, C(3) (*i*Gln)), 27.98 (d, C(2) (Cp)), 27.0 (t, Oct), 23.6 (t, Oct), 18.6 (q, Me), 17.9 (q, Me), 14.3 (q, Me (Oct)), 12.5 (dd, C(3) (Cp)); MS (e.i., 70 eV): *m*/*z*=560 (5%), 452 (1%), 363 (1%), 346 (3%), 325 (1%), 297 (4%), 282 (1%), 255 (11%), 237 (4%), 226 (4%), 198 (6%), 192 (4%), 181 (4%), 127 (100%). Anal. Calcd for $C_{29}H_{44}O_7N_4$ (560.321): C, 62.12; H, 7.91; N, 9.99. Found: C, 61.98; H, 7.89; N, 10.10.

3.1.18. *trans*-(2*R*)-2-[2-(Octanoylamino)cyclopropyloxy] propionyl-L-alanyl-D-isoglutamine (18a). Hydrogenolysis of **16a** (45 mg, 0.08 mmol) in ethanol (10 ml) in the presence of Pd/C (10%, 20 mg) followed by chromatography (silica gel, chloroform/methanol/acetic acid, 85:10:5) gave **18a** (33 mg, 86%) as a white solid; mp: 200–210 °C (decomp.); R_f ($CHCl_3$/MeOH/AcOH, 85:10:5) 0.35; $[\alpha]_D$ 31.8° (*c* 1.02, MeOH); IR (KBr): ν=3430s, 2930m, 2860w, 1655m, 1615s, 1570s, 1555s, 1420s, 1280m, 1050m, 1020m cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ=8.67 (br, 1H, NH), 8.12 (br, 1H, NH), 8.02 (d, $^3J_{H,H}$=6.6 Hz, 1H, NH), 7.31 (br, 1H, NH), 7.00 (br, 1H, NH), 4.22 (qd, $^3J_{H,H}$=6.8 Hz, 1H, CH (Ala)), 4.17 (q, $^3J_{H,H}$=6.6 Hz, 1H, CH (Lac)), 4.07–4.02 (m, 1H, CH (*i*Gln)), 3.38–3.33 (m, 1H, H–C(1) (Cp)), 2.61–2.56 (m, 1H, H–C(2) (Cp)), 2.04–1.97 (m, 2H+2H, H–C(4) (*i*Gln), H–C(2) (Oct)), 1.90–1.70 (m, 2H, H–C(3) (*i*Gln)), 2.11–1.97 (m, 2H+1H, H–C(2) (Oct), 1.47–1.42 (m, 2H, H–C(3) (Oct)), 1.23–1.18 (m, 3H+3H+8H, Me, Me, Oct), 0.99–0.94 (m, 1H, H_A–C(3) (Cp)), 0.84 (t, $^3J_{H,H}$=6.6 Hz, 3H, Me (Oct)), 0.71–0.66 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=177.8 (s, C=O), 176.9 (s, C=O), 175.5 (s, C=O), 175.0 (s, C=O), 77.1 (d, C(2) (Lac)), 59.1 (d, C(1) (Cp)), 54.6 (d, C(2) (*i*Gln)), 50.8 (d, C(2) (Ala)), 36.9 (t, C(2) (Oct)), 32.9 (t, C(3) (Oct)), 32.1 (t, C(4) (*i*Gln)), 30.3 (t, Oct), 30.1 (t, Oct), 29.8 (d, C(2) (Cp)), 29.2 (t, C(3) (*i*Gln)), 26.9 (t, Oct), 23.7 (t, Oct), 18.8 (q, Me), 17.6 (q, Me), 15.2 (dd, C(3) (Cp)), 14.4 (q, Me (Oct)); HPLC-MS (ESI, 4.1 kV, 8 μl/min, N_2, methanol): *m*/*z*=509.5 $[MK]^+$ (100%), 493.5 $[MNa]^+$ (2.5%); HRMS Calcd for $C_{22}H_{38}O_7N_4$: 470.2740. Found: 470.2741. Anal. Calcd for $C_{22}H_{38}O_7N_4$ (470.274): C, 56.15; H, 8.14; N, 11.91. Found: C, 55.93; H, 7.95; N, 11.79.

3.1.19. *trans*-(2*R*)-2-[2-(Octanoylamino)cyclopropyloxy] propionyl-L-alanyl-D-isoglutamine (18b). Hydrogenolysis of **16b** (75 mg, 0.13 mmol) in ethanol (10 ml) in the presence of Pd/C (10%, 20 mg) followed by chromatography (silica gel, chloroform/methanol/acetic acid, 85:10:5) gave **18b** (55 mg, 87%) as a white solid; mp: ca. 200–209 °C (decomp.); R_f ($CHCl_3$/MeOH/AcOH, 85:10:5) 0.35; $[\alpha]_D$ 12.5° (*c* 1.03, MeOH); IR (KBr): ν=3405s, 3070w, 2930m, 2855w, 1740m, 1645s, 1545m, 1450m, 1375w, 1310w, 1245w, 1170w, 1090w cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.83 (d, $^3J_{H,H}$=6.3 Hz, 1H, NH), 7.15 (d, $^3J_{H,H}$=7.2 Hz, 1H, NH), 6.93 (br, 1H, NH), 5.55 (br, 1H, NH), 5.47 (br, 1H, NH), 4.43–4.39 (m, 1H, CH (*i*Gln)), 4.28 (q, $^3J_{H,H}$=6.4 Hz, 1H, CH (Lac)), 4.21 (qd, $^3J_{H,H}$=6.7 Hz, 1H, CH (Ala)), 3.32–3.27 (m, 1H, H–C(1) (Cp)), 2.84–2.79 (m, 1H, H–C(2) (Cp)), 2.55–2.48 (m, 1H, H_A–C(4) (*i*Gln)), 2.44–2.38 (m, 1H, H_B–C(4) (*i*Gln)), 2.24–2.16 (m, 1H, H_A–C(3) (*i*Gln)), 2.11–1.97 (m, 2H+1H, H–C(2) (Oct), H_B–C(3) (*i*Gln)), 1.62–1.55 (m, 2H, H–C(3) (Oct)), 1.38 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me), 1.36 (d, $^3J_{H,H}$=6.6 Hz, 3H, Me), 1.28–1.22 (m, 8H, Oct), 1.12–1.07 (m, 1H, H_A–C(3) (Cp)), 0.85 (t, $^3J_{H,H}$=6.8 Hz, 3H, Me (Oct)), 0.79–0.74 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ= 178.0 (s, C=O), 176.4 (s, C=O), 175.9 (s, C=O), 175.4 (s, C=O), 175.1 (s, C=O), 77.4 (d,

C(2) (Lac)), 59.6 (d, C(1) (Cp)), 53.6 (d, C(2) (*i*Gln)), 50.7 (d, C(2) (Ala)), 36.8 (t, C(2) (Oct)), 32.8 (t, C(3) (Oct)), 31.1 (t, C(4) (*i*Gln)), 30.2 (t, Oct), 30.0 (t, Oct), 29.6 (d, C(2) (Cp)), 28.0 (t, C(3) (*i*Gln)), 26.8 (t, Oct), 23.6 (t, Oct), 18.5 (q, Me), 17.7 (q, Me), 14.7 (dd, C(3) (Cp)), 14.3 (q, Me (Oct)); MS (e.i., 70 eV): *m*/*z*=452 (1%), 342 (2%), 325 (3%), 297 (14%), 273 (1%), 255 (14%), 226 (2%), 198 (8%), 183 (9%), 144 (21%), 127 (100%); HRMS Calcd for $C_{22}H_{38}O_7N_4$: 470.2740. Found: 470.2741. Anal. Calcd for $C_{22}H_{38}O_7N_4$ (470.274): C, 56.15; H, 8.14; N, 11.91. Found: C, 55.97; H, 8.09; N, 11.74.

3.1.20. *cis*-(2*R*)-2-[2-(Octanoylamino)cyclopropyloxy] propionyl-L-alanyl-D-isoglutamine (19a). Hydrogenolysis of **17a** (80 mg, 0.14 mmol) in ethanol (20 ml) in the presence of Pd/C (10%, 20 mg) followed by chromatography (silica gel, chloroform/methanol/acetic acid, 85:10:5) gave **19a** (66 mg, 100%) as a white solid; mp: 198–209 °C (decomp.); R_f ($CHCl_3$/MeOH/AcOH, 85:10:5) 0.20; $[\alpha]_D$ −15.5° (*c* 0.57, MeOH); IR (KBr): ν=3425s, 2930m, 2860w, 1655s, 1545s, 1420s, 1175w, 1025w cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=8.64 (br, 1H, NH), 8.00 (br, 1H, NH), 7.99 (br, 1H, NH), 7.35 (br, 1H, NH), 6.98 (br, 1H, NH), 4.25 (qd, $^3J_{H,H}$=7.1 Hz, 1H, CH (Ala)), 4.08–4.03 (m, 1H, CH (*i*Gln)), 3.85 (q, $^3J_{H,H}$=6.7 Hz, 1H, CH (Lac)), 3.28–3.24 (m, 1H, H–C(1) (Cp)), 2.66–2.60 (m, 1H, H–C(2) (Cp)), 2.09 (t, $^3J_{H,H}$=7.4 Hz, 2H, H–C(2) (Oct)), 2.02 (t, $^3J_{H,H}$=7.1 Hz, 2H, H–C(4) (*i*Gln)), 1.90–1.82 (m, 1H, H_A–C(3) (*i*Gln)), 1.74–1.68 (m, 1H, H_B–C(3) (*i*Gln)), 1.51–1.46 (m, 2H, H–C(3) (Oct)), 1.28–1.22 (m, 3H+8H, Me+Oct), 1.17 (d, $^3J_{H,H}$=6.6 Hz, 3H, Me), 0.91–0.85 (m, 1H, H_A–C(3) (Cp)), 0.84 (t, $^3J_{H,H}$=6.8 Hz, 3H, Me (Oct)), 0.72–0.68 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=178.2 (s, C=O), 176.5 (s, C=O), 175.8 (s, C=O), 175.2 (s, C=O), 169.6 (s, C=O), 77.8 (d, C(2) (Lac)), 55.8 (d, C(1) (Cp)), 53.8 (d, C(2) (*i*Gln)), 50.6 (d, C(2) (Ala)), 36.8 (t, C(2) (Oct)), 32.8 (t, C(3) (Oct)), 31.3 (t, C(4) (*i*Gln)), 30.3 (t, Oct), 30.1 (t, Oct), 28.3 (d, C(2) (Cp)), 28.1 (t, C(3) (*i*Gln)), 27.0 (t, Oct), 23.6 (t, Oct), 18.9 (q, Me), 17.9 (q, Me), 14.3 (q, Me (Oct)), 11.8 (dd, C(3) (Cp)); HPLC-MS (ESI, 4.1 kV, 8 μl/min, N_2, methanol): *m*/*z*=1487.2 $[M_3K_2-H]^+$ (61%),1017.2 $[M_2K_2-H]^+$ (28%), 979.3 $[M_2K]^+$ (100%), 509.3 $[MK]^+$ (95%), 471.4 $[MH]^+$ (10%); HRMS Calcd for $C_{22}H_{38}O_7N_4$: 470.2740. Found: 470.2741. Anal. Calcd for $C_{22}H_{38}O_7N_4$ (470.274): C, 56.15; H, 8.14; N, 11.91. Found: C, 56.00; H, 8.10; N, 11.99.

3.1.21. *cis*-(2*R*)-2-(2-(Octanoylamino)cyclopropyloxy) propionyl-L-alanyl-D-isoglutamine (19b). Hydrogenolysis of **17b** (53 mg, 0.095 mmol) in ethanol (40 ml) in the presence of Pd/C (10%, 20 mg) followed by chromatography (silica gel, chloroform/methanol/acetic acid, 85:10:5) afforded **19b** (38 mg, 85%) as a white solid; mp: 196–204 °C (decomp.); R_f ($CHCl_3$/MeOH/AcOH, 85:10:5) 0.20; $[\alpha]_D$ 17.4° (*c* 0.95, MeOH); IR (KBr): ν=3430s, 2930w, 2855w, 1655s, 1550s, 1420s, 1175w, 1020w cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=8.71 (br, 1H, NH), 7.98 (br, 1H, NH), 7.80 (d, $^3J_{H,H}$=7.5 Hz, 1H, NH), 7.33 (br, 1H, NH), 6.98 (br, 1H, NH), 4.24 (qd, $^3J_{H,H}$=6.7 Hz, 1H, CH (Ala)), 4.08–4.02 (m, 1H, CH (*i*Gln)), 3.91 (q, $^3J_{H,H}$= 6.6 Hz, 1H, CH (Lac)), 3.47–3.43 (m, 1H, H–C(1) (Cp), determined in CD_3OD), 2.60–2.55 (m, 1H, H–C(2) (Cp)), 2.09–1.99 (m, 4H, H–C(4) (*i*Gln), H–C(2) (Oct)), 1.88–1.82 (m, 1H, H_A–C(3) (*i*Gln)), 1.74–1.68 (m, 1H, H_B–C(3) (*i*Gln)), 1.48–1.40 (m, 2H, H–C(3) (Oct)), 1.25–1.21 (m, 6H+8H, 2×Me+Oct), 0.92–0.87 (m, 1H, H_A–C(3) (Cp)), 0.84 (t, $^3J_{H,H}$=6.7 Hz, 3H, Me (Oct)), 0.72–0.68 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (125 MHz, CD_3OD): δ=178.2 (s, C=O), 175.7 (s, C=O), 175.0 (s, C=O), 169.6 (s, C=O), 77.8 (d, C(2) (Lac)), 55.5 (d, C(1) (Cp)), 54.5 (d, C(2) (*i*Gln)), 50.6 (d, C(2) (Ala)), 36.9 (t, C(2) (Oct)), 32.9 (t, C(3) (Oct)), 30.3 (t, Oct, C(4) (*i*Gln)), 30.1 (t, Oct), 29.3 (t, C(3) (*i*Gln)), 28.1 (d, C(2) (Cp)), 27.0 (t, Oct), 23.6 (t, Oct), 18.7 (q, Me), 17.9 (q, Me), 14.4 (q, Me (Oct)), 12.5 (dd, C(3) (Cp)); HPLC-MS (ESI, 4.1 kV, 8 μl/min, N_2, methanol): *m*/*z*=509.3 $[MK]^+$ (n100%); HRMS Calcd for $C_{22}H_{38}O_7N_4$: 470.2740. Found: 470.2741. Anal. Calcd for $C_{22}H_{38}O_7N_4$ (470.274): C, 56.15; H, 8.14; N, 11.91. Found: C, 56.10; H, 8.24; N, 11.73.

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